Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: technical results, clinical outcome and factors potentially influencing survival

ABSTRACT

Background: the purpose of this study was to retrospectively assess the technical and clinical outcomes, overall survival and prognostic factors for prolonged survival after yttrium-90 radioembolization as a salvage therapy for patients with chemorefractory liver-only or liver-dominant colorectal metastases.

Material and Methods: from January 2005 till January 2014, all the patients selected for yttrium-90 radioembolization to treat chemorefractory colorectal liver metastases were identified. Demographic, laboratory, imaging and dosimetry data were collected. Post-treatment technical and clinical outcomes were analysed as well as overall survival; finally several factors potentially influencing survival were analysed.

Results: 88 patients were selected for angiographic workup; 71 patients (81%) finally underwent catheter-directed yttrium-90 microsphere infusion into the hepatic artery 25 days (standard deviation 13 days) after angiographic workup. Median infused activity was 1809 MBq; 30-day toxicity included: fatigue (n=39; 55%), abdominal discomfort (n=33; 47%), nausea (n=5; 7%), fever (n=14; 20%), diarrhea (n=6; 9%), liver function abnormalities and elevated bilirubin (transient) (n= 3; 4%). Gastric ulcer was found in 5 patients (7%). A late complication was radioembolization-induced portal hypertension (REIPH) in 3 patients (4%). Median time to progression in the liver was 4.4 months. Estimated survival at 6 and 12 months was 65% and 30%, respectively, with a 50% estimated survival after 8.0 months in this group of chemorefractory patients. Prognostic factors for worse survival were high preprocedural bilirubin, alkaline phosphatase and tumor volume levels.

Conclusion: yttrium-90 microsphere radioembolization for chemorefractory colorectal liver metastases has an acceptable safety profile with a 50% estimated survival after 8.0 months. Pretreatment high bilirubin, alkaline phosphatase and tumor volume levels were associated with early death.

Key words: outcome, liver metastases, selective internal radiation therapy (SIRT)

INTRODUCTION

Colorectal cancer is the second most common cancer in Europe and 15 – 25% of patients develop liver metastases. If these patients are ineligible for local ablative therapies like radiofrequency ablation (RFA) or for surgical resection, chemotherapeutic treatment remains the therapeutic mainstay for this patient population with overall survival beyond 2 years [1-2]. For more than a decade, the transarterial administration of radioactive yttrium-90 (^{90}Y) microspheres (called selective internal radiation therapy (SIRT) or radioembolization) has been under evaluation as a promising additional, locoregional tool in the management of patients with liver-only or liver-dominant metastatic colorectal cancer (mCRC). Recently, it has been demonstrated that the combination of 5-fluorouracil (5-FU) and ^{90}Y radioembolization results in improved survival compared to treatment with 5-FU alone [3] in chemorefractory patients with liver-only or liver-dominant mCRC. Based on these findings, radioembolization is recommended in the guidelines from the European Society of Medical Oncology (ESMO) for patients with liver-limited metastases in whom the available chemotherapeutic options have failed [2].

Several observational cohort studies [4-10] as well as a few meta-analyses dealing with radioembolization for chemorefractory mCRC have been published, all of them demonstrating the relative safety of the radioembolization technique and the potential for better survival. However, only limited data on late toxicity of ^{90}Y in this patient population are available [11-13]. Additionally, little information is available about potential prognostic factors for prolonged survival. Postprocedural radiological response seems to be the best prognostic parameter for better survival. However, no data are available on the potential for use of preprocedural (laboratory and radiological) parameters for survival prognosis.

In this manuscript, we report the early and late side-effects of radioembolization in a 'real world' patient population with chemorefractory mCRC at a tertiary referral centre for digestive cancers over a 9 year time span. Furthermore, we report overall survival and have analysed the prognostic potential of preprocedural factors for prediction of improved survival.

MATERIALS AND METHODS

Patient demographics

From January 2005 until January 2014, 88 patients with chemorefractory colorectal liver metastases were selected for ^{90}Y radioembolization by the institutional tumor board for digestive cancers at University Hospitals Leuven, including medical, surgical and radiation oncologists, pathologists, interventional and diagnostic radiologists and nuclear medicine physicians.

All patients presented with colorectal liver metastases refractory to several lines of chemotherapy, including oxaliplatin and irinotecan-based schemes, with no indication for surgical resection or local ablative treatments. Tumor load within the liver as well as extrahepatic metastatic spread were assessed by body computed tomography (CT) and/or ^{18}F-fluorodeoxyglucose positron emission tomography (PET) with or without CT.

Patients gave informed consent for the ^{90}Y radioembolization workup and treatment after being informed about the different steps of the treatment and the effect of radiation on the metastases and the residual liver parenchyma. The local Ethics Committee gave approval for this retrospective study.

Inclusion criteria for patient selection were:

- confirmed histological diagnosis of colorectal cancer
- unresectable liver metastases
- ECOG status 0-1
- Liver-limited or liver-predominant disease
- no previous external beam radiotherapy to the liver
- adequate bone marrow reserve, including granulocytes > $1500*10^9$/L and platelets > $60.000*10^9$/L
- no contraindication for selective angiography, including normal renal function (serum creatinine < 1.8 mg/ml) and no allergy to iodinated contrast medium
- bilirubin level < 2.5 mg/ml
- lung shunt fraction (LSF) < 20% assessed during post-angiographic workup ^{99m}technetium-macroaggregated albumin (^{99m}Tc-MAA) scintigraphy

Radiological technique

The interventional radiological technique for ^{90}Y delivery into the liver tumors consists of an angiographic workup including ^{90m}Tc-MAA planar scintigraphy and SPECT (/CT) and transcatheter infusion of the ^{90}Y-loaded microspheres into the hepatic artery a few weeks later, performed in accordance with previously published guidelines and technical angiographic reviews [14,15].

Briefly, under local anesthesia, access is gained to the right common femoral artery with use of a 4 French (F) introducer sheath (Boston Scientific, Natick, MA, USA). Selective angiography of the celiac trunk and superior mesenteric artery is performed using a 4 F Simmons 1 catheter (Impress®, Merit Medical, South Jordan, UT, USA). Enterohepatic arteries are identified and, if indicated, coil embolized (Target microcoils, Boston Scientific, Natick, MA, USA or Microtornado, Cook Medical, Bloomington, IN, USA) through a microcatheter (Progreat 2.7, Terumo Europe, Leuven, Belgium or Maestro 2.4, Merit Medical, South Jordan, UT, USA). Finally, the microcatheter is positioned in the proximal lobar hepatic artery/arteries, which is the same position as for the ^{90}Y microsphere infusion, and a diagnostic volume of ^{99m}Tc-MAA is injected. Typically, 100 mega-Becquerel (MBq) is injected in the right lobe and 50 MBq in the left lobe of the liver.

After sheath removal and femoral compression for 10 minutes, the patient is immediately referred to the nuclear medicine department for planar scintigraphy within one hour after ^{99m}Tc-MAA injection to determine the LSF and SPECT (/CT) evaluation for the assessment of extrahepatic and intratumoral ^{99m}Tc-MAA deposition [16].

The selective internal radiation therapy (SIRT) procedure was then performed between 2 and 5 weeks after the angiographic workup with the use of resin ^{90}Y microspheres (SIR spheres, Sirtex Inc, Cosgrove, Australia). The SIRT procedure, also performed under local anesthesia, included correct positioning of the tip of the microcatheter within the hepatic artery/arteries at the same position as the injection of ^{99m}Tc-MAA during workup. In no patient, (super-) selective infusion of ^{90}Y microspheres into a tumor feeding artery was performed. No chemotherapeutic drugs were administered immediately before or after the SIRT procedure; anti-emetics and morphine derivatives were given when required. Steroids, proton pump inhibitors or antibiotics were not systematically administered.

All bilobar SIRT procedures were performed in one session.

^{90}Y microsphere activity calculation

Activity calculation was mainly performed using the body surface area (BSA) method. In patients with diffuse bilobar disease the activity injected was the one calculated using the BSA method. Initially these values were reduced if the LSF was >10% (10-15%: reduction to 80%; >15%-20%: 60%) but in patients treated later the activity was only reduced if the calculated dose would result in a lung dose of more than 30 Gy, with a reduction leading to a 30 Gy lung dose. In patients with unilobar disease in which activity escalation could be performed the partition model was used.

^{90}Y brehmsstrahlung imaging

Patients were imaged on the day of the ^{90}Y microsphere infusion or the next day. Brehmsstrahlung imaging was performed on the same gamma cameras as used for the ^{99m}Tc-MAA scintigraphy. No ^{90}Y PET imaging was performed as we did not have a time-of-flight PET camera during the time period studied.

Follow-up

All patients were clinically followed up by the attending medical oncologist and by their general practitioner. Early complications were defined as treatment-related complications occurring within 30 days after infusion of ^{90}Y microspheres. Late complications are defined as ^{90}Y-related side effects occurring later than 30 days after infusion of ^{90}Y microspheres. Radiological follow-up was performed with CT or ^{18}F-FDG-PET-CT with a time interval of 2 months until progression of disease; additional CT-scan was performed if a new clinical event occurred. Once the patient presented with progression of disease, it was decided, after

discussion with the patient and his/her family, if further treatment and/or radiological follow-up was performed.

Grading of side effects was based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Study design

Aims of the study were assessment of time to tumor progression in the liver, overall survival after ^{90}Y microsphere radioembolization, tolerability of the treatment and late complications related to ^{90}Y infusion. Additionally, several factors potentially influencing survival were analysed. The factors are discrete variables including synchronous versus metachronous liver metastases and total activity versus reduced activity delivery; continuous variables analysed were: laboratory data including platelet count, carcinoembryonic antigen, bilirubin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase and LSF, total administered activity in MBq and total tumor volume.

Statistical analysis

Kaplan-Meier estimates were used for overall survival curves; frequencies and percentages are presented for categorical variables. Mean and standard deviation (STD) as well as median and quartiles are given for continuous variables. Univariable analysis of the prognostic value of variables for overall survival after ^{90}Y radioembolization was carried out using Cox proportional hazards regression. Effects of continuous variables were explored by comparing linear and non-linear associations, including quadratic and cubic splines based trends.

A multivariable prediction model for overall survival after ^{90}Y radioembolization was based on the multiple imputation procedure for model building, given the considerable number of missing values for some predictor variables. Missing values were imputed 10 times, creating

10 complete data sets. Imputation was based on linear or logistic regression for continuous and binary variables, respectively, and on predictor variables. Given the fact that all selected variables in the final model were completely observed (no missing values), interference is based on the observed data only.

The Concordant Probability Estimate (CPE) or C-index is determined as an indicator of the discriminatory power of the risk prediction model for overall survival after ^{90}Y radioembolization. This index takes values between 0.5 (discriminator no better than random) and 1 (perfect discrimination). Interpretation is similar to the (area under the curve) (AUC) or C-index for binary responses, indicating the probability that the predictions for a random pair of subjects are concordant with their outcomes [17].

All tests are two-sided and a 5% significance level is assumed for all tests. All analyses have been performed using SAS software, version 9.3 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Initially, 88 patients were selected for angiographic workup; however 17 out of these 88 patients (19%) were excluded from further SIRT therapy based on an LSF of > 20% (n=7); leakage of ^{99m}Tc-MAA to the gastroduodenal area, not correctable by repeat angiography and coil embolization (n=1), prior external beam radiotherapy to the liver unknown at the time of angiographic workup and progression of disease resulting in excessive extrahepatic disease during the time period between angiographic workup and the SIRT procedure (n=8). Overall, 71 patients underwent both angiographic workup and transcatheter SIRT therapy and these patients are studied below.

Demographic data

The patients' demographics are summarized in Table I. The majority of included patients were men, presenting with synchronous, bilobar colorectal liver metastases with no extrahepatic tumor load.

Laboratory data, including platelet count, carcinoembryonic antigen (CEA), bilirubin, kidney and liver function tests are summarized in Table II.

All patients (n=71 ; 100%) had progressed on second line chemotherapy ; 44 out of 71 patients (62%) had progressed on third line chemotherapy. In total 40 out of 71 patients (56%) received cetuximab prior to ^{90}Y radioembolization.

At the time inclusion for SIRT-therapy, 2 out of 71 included patients (3%) had a bilirubine level > 2.5 mg/ml and 20 out of 71 patients (28%) had a bilirubine level > 1 mg/dl.

Radiological and nuclear medicine data

During angiographic workup, the gastroduodenal artery was coiled in 60 patients (85%), the right gastric artery in 30 patients (42%), the left gastric artery in 3 patients (4%), a pancreatic artery in 2 patients (3%), the supraduodenal artery in 1 patient (1%) and the phrenic artery in 1 patient (1%). Finally, flow redistribution was obtained after coil embolization of the left hepatic artery in 4 patients (6%) and of the accessory branch to segment 4 in 2 patients (3%).

The LSF based on the ^{99m}Tc-MAA scintigraphy had a mean value of 8% with a standard deviation of 3.5%, a median value of 7.8% with an IQR between 5.9% and 9.8% and a range between 3% and 19% (Fig. 1). The mean time interval between the workup angiographic procedure and the ^{90}Y infusion therapy was 25 days (standard deviation: 13 days).

The total liver volume, liver tumor volume, diameter of the largest liver metastasis, the number of patients treated with a reduced activity and the total activity of ^{90}Y microspheres administered to the patients are summarized in Table III.

Technical and clinical outcome

1. Early and late ^{90}Y microsphere related toxicity

^{90}Y microsphere related toxicity detected during the first month after treatment included: NCI-CTCAE grade 1 side effects, including fatigue (n=39 ; 55%) and fever (n=14 ; 20%); NCI-CTCAE grade 2 side effects, including abdominal discomfort (n=33 ; 47%), nausea (n=5 ; 7%) and diarrhea (n=6 ; 9%) and NCI-CTCAE grade 3 side effect, including procedure-related liver insufficiency, defined as twofold increase in bilirubin level within 30 days after ^{90}Y infusion (n=3 ; 4%).
Late complications, defined as ^{90}Y -related side effects detected later than 30 days after the ^{90}Y infusion were NCI-CTCAE grade 2 side effects, including gastric ulcers, potentially related to non-target infusion of ^{90}Y -loaded microspheres into the gastroduodenal vasculature, which were endoscopically confirmed in 5 patients (7%). One patient required a partial gastrectomy for definitive management of these ulcers. Finally, NCI-CTCAE grade 3 late complications were identified in another 3 patients (4%). These late adverse events were fibrotic/cirrhotic changes in the liver parenchyma, associated with symptoms of portal hypertension (radioembolization-induced portal hypertension, REIPH): one patient presented with variceal upper gastrointestinal bleeding, while 2 other patients presented with benign, refractory ascites respectively 19, 19 and 12 months after initial ^{90}Y radioembolization (Fig. 2a-b, Fig. 3a-b). The upper gastrointestinal, variceal bleeding was managed using endoscopic techniques; the refractory ascites by repeated parascenteses.

2. Disease free survival, time to tumor progression in the liver and overall survival.

Radiological follow-up data for the assessment of disease free survival and time to tumor progression in the liver was available in 61 out of 71 patients (86%), demonstrating a median disease free survival of 3 months (mean 4.6 months, standard deviation 4.1 months) and a median time to progression in the liver of 4 months (mean 6.0 months, standard deviation 5.1

months). One patient (1.5%) could be downstaged for combined surgical segmentectomy in the right liver lobe and radiofrequency ablation in the left liver lobe. Overall, estimated survival at 6 and 12 months is 65% and 30% respectively with a 50% estimated mortality after 8.0 months (Table IV and Fig. 4).

3. Factors potentially influencing survival

Univariate analysis, summarized in Table V, demonstrates an increased risk of early mortality for increased baseline alkaline phosphatase values; a non-linear correlation was found between bilirubin levels and total tumor volume and prolonged survival: patients with the lowest baseline values for bilirubin and total tumor volume had a lower risk of early mortality, whereas intermediate values had the highest risk of early death (Fig. 5, Fig. 6). Increased AST levels are associated with a higher risk of early mortality, but the correlation is non-linear with a flattening of the effect for the lowest and highest levels (Fig. 7).
Finally, multivariate analysis demonstrates a linear increase in early mortality after SIRT in patients with higher baseline alkaline phosphatase levels: for each increase by 10 units, the risk of death rises by 1% (Fig. 8). The CPE value of this model is 0.65, meaning that in 65% of patient pairs the model will give a correct prognosis for which of the two patients the best survival can be predicted (Table VI).

DISCUSSION

This report confirms the low complication rate related to the infusion of ^{90}Y microspheres into the liver, in line with other studies dealing with SIRT for treatment of colorectal liver metastases: prolonged abdominal pain, fatigue and radiation-induced gastroduodenal ulcers were identified in respectively 46%, 55% and 7%, which is within the range of other

published experiences [12]. We also identified 3 patients (4%) presenting with a significant increase in bilirubin levels within 30 days after the ^{90}Y infusion. This phenomenon may be related to radioembolization-induced liver disease, although rapid progression of liver disease may potentially also result in elevated bilirubin levels. Three patients (4%) presented with cirrhosis-like changes in the liver parenchyma, associated with severe symptoms of portal hypertension, including refractory ascites (n=2) and variceal upper gastrointestinal bleeding (n=1), respectively 19, 12 and 12 months after ^{90}Y treatment. This complication, which we defined as radioembolization-induced portal hypertension, is most probably an extreme clinical presentation of the radiation-induced liver fibrosis described by Jacobs et al. [11]. Potentially, this late complication might be avoided if these patients had received corticosteroids as suggested by Sangro et al [18]. As these symptoms of radioembolization-induced portal hypertension were identified at one year or later after SIRT-therapy, the potential incidence of this side effect might be much higher than 4% if patients with a potential better survival prognosis will be treated with SIRT, like patients treated with SIRT in an earlier stage of their disease.

The general overall survival after ^{90}Y radioembolization in our cohort of chemorefractory colorectal cancer patients shows a median overall survival of 8.0 months and 30% of the treated patients were still alive after 1 year of follow-up. In a systematic review, Saxena et al. [19] found an overall survival for patients with colorectal liver metastases who were treated with ^{90}Y microspheres ranging from 8.0 months to 36 months. The lowest survival results were found in the patient populations previously treated with the most lines of intravenous chemotherapy, as in our patient population [20]. Additionally, we did not administer an intravenous 5-FU infusion immediately after the ^{90}Y infusion as described by Hendlisz et al. [3], which might also have a beneficial effect on the survival outcome. The median overall survival of 8.0 months after ^{90}Y -radioembolization for colorectal liver metastases in patients

refractory to all types of chemotherapy seems to be somewhat better than the overall survival after best supportive care (5.0 months) or after regorafenib (6.4 months) (26). However, a prospective, randomized trial comparing ^{90}Y to Regorafenib might give the answer to better determine the place of these treatments in patients with colorectal metastases, refractory to all types of currently available chemotherapies.

The median time to tumor progression in the liver was 4.4 months, which is in line with other studies dealing with the same patient population [2]. In this cohort of patients with chemorefractory colorectal liver metastases, downstaging to surgical resection remains rare: only 1 patient was finally able to be resected and these data confirm those obtained by Cosimelli et al. [5].

We also found a substantial number of patients (n=19) who were excluded from ^{90}Y microsphere infusion after the workup procedure. Exclusion from ^{90}Y microsphere infusion was mainly related to a high liver-lung shunt of > 20% (n=7) or to rapid disease progression during the interval between angiographic workup and ^{90}Y radioembolization (n=8). The mean time interval seems to be relatively long (25 days) and the number of excluded patients could possibly be reduced if a shorter time interval could be considered.

We also analysed several pre-interventional biochemical and imaging parameters which potentially influence the overall survival. In a univariable analysis, higher alkaline phosphatase, AST and ALT values were associated with a higher risk of early mortality; for bilirubin and total tumor volume values, better survival seems to be observed for the lowest values while intermediate values were associated with an increased risk of early mortality. A flattening or even a discrete decrease in early deaths was noted for the highest pre-treatment levels of bilirubin and total tumor load. Based on these results, patients with both borderline high bilirubin and borderline high tumor volume levels should not be excluded from ^{90}Y radioembolization, which is in line with the results of Jacobs et al. [6]. However, other studies suggest a higher risk of early mortality in patients with a higher tumor burden [21-24].

The presented study cannot confirm the results of Deipolyi et al. [25] showing an increased risk of early widespread metastatic growth and subsequently early mortality in those patients with a high liver-lung shunt (p=0.1087). Deipolyi et al [25] hypothesize that a higher liver-lung shunt is associated with larger vascular, intratumoral shunts between the hepatic artery and hepatic vein, thereby facilitating malignant cell migration from the liver to the lungs and other organs.

In a multivariate analysis, a higher alkaline phosphatase level and an intermediate bilirubin level are associated with a higher risk of early mortality.

In conclusion, this study confirms the good safety profile of ^{90}Y microspheres administered in the hepatic artery for the treatment of colorectal liver metastases with an overall survival of 8 months in chemorefractory mCRC patients with liver-limited or liver-predominant metastases. However, a relatively high number of patients were excluded from further treatment after the workup mainly due to a high liver-lung shunt or rapid disease progression during the time period between the workup and ^{90}Y microsphere administration.

Pre-interventional higher bilirubin, alkaline phosphatase and AST levels as well as a higher pretreatment tumor burden are associated with higher risk of early mortality.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR's CONTRIBUTION

GM conceived of the study, took care of the data acquisition, drafted the manuscript, and took care of the supervision. CD conceived of the study, took care of the data acquisition, and drafted the manuscript, together with GM. AL performed the statistical analysis. CV helped with the data acquisition. KH also helped with the data acquisition and took care of the supervision, together with GM. SH, GDH, XS, BT, RA, HP, DV and VV helped with the data acquisition. EVC took care of the supervision. All authors read and approved the final manuscript.

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Table I: Demographic data of included patients

Variable	Statistic	Total = 71
Sex		
M	n/N (%)	51/71 (72%)
F	n/N (%)	20/71 (28%)
Age	N	71
	Mean	62.5
	STD	9.5
	Median	62.0
	IQR	(56 – 70)
	Range	(42 – 82)
Synchronous/metachronous		
Metachronous	n/N (%)	23 (32%)
Synchronous	n/N (%)	48 (68%)
Uni/bilobar involvement		
Unilobar	n/N (%)	13 (18%)
Bilobar	n/N (%)	58 (82%)
Extrahepatic disease		
No	n/N (%)	49 (69%)
Yes	n/N (%)	22 (31%)
Previous liver surgery	n/N (%)	10 (14%)
Previous RF ablation	n/N (%)	6 (8%)
Previous FOLFOX	n/N (%)	69 (97%)
Previous FOLFIRI	n/N (%)	67 (94%)
Previous biologicals		
Bevacizumab	n/N (%)	29 (41%)
Cetuximab	n/N (%)	40 (56%)

IQR: interquartile range
STD: standard deviation

Table II: Laboratory data before SIRT

Variable	statistic	All
Platelet count n*10^9/L	N	71
	Mean	253
	STD	116
	Median	237
	IQR	(168 – 316)
	Range	(88 – 694)
CEA, µg/L	N	71
	Mean	853
	STD	2918
	Median	119
	IQR	(36.5 – 692)
	Range	(1.7 – 23890)
Bilirubin mg/dL	N	71
	Mean	0.9
	STD	0.57
	Median	0.8
	IQR	(0.5 – 1.1)
	Range	(01 – 2.7)
Creatinine mg/dL	N	71
	Mean	0.8
	STD	0.25
	Median	0.8
	IQR	(0.7 – 1.0)
	Range	(0.4 – 1.8)
AST U/L	N	71
	Mean	53
	STD	44
	Median	40
	IQR	(32 – 55)
	Range	(19 – 258)
ALT U/L	N	71
	Mean	42
	STD	34
	Median	31
	IQR	(21 – 50)
	Range	(4 – 204)
Alk.phosph. U/L	N	71
	Mean	548
	STD	401
	Median	410
	IQR	(266 – 714)

IQR: interquartile range
STD: standard deviation
AST: aspartate transaminase
ALT: alanine transaminase
Alk.phosph.: alkaline phosphatase

Table III: liver volume, tumor volume and total administered activity

Variable	statistic	all
Total liver tumor volume/total liver volume	N	49
	Mean	34.9
	STD	28.1
	Median	26.7
	IQR	14.5 - 50
	Range	0.7 - 120
Diameter of the largest liver metastasis (mm)	N	71
	Mean	68.2
	STD	28.12
	Median	69.0
	IQR	(45.0; 85.0)
	Range	(23.0; 146.0)
Full versus reduced administered activity		
Activity reduction	n/N (%)	6/48 (12.5%)
Full activity	n/N (%)	42/48 (87.5%)
Total administered activity (MBq)	N	66
	Mean	1819
	STD	309
	Median	1810
	IQR	(1647 – 1994)
	Range	(818 – 2454)

STD: standard deviation
IQR: interquartile range

Table IV: estimated survival rates of the studied patients

Survival in months since SIRT therapy

		95% confidence interval (CI)	
Months	% survival	lower limit	upper limit
6	65	55	73
12	30	24	36
18	20	16	25
24	6	4	7

Mortality in months since SIRT therapy

		95% confidence interval (CI)	
Percentile	months since ^{90}Y	lower limit	upper limit
25%	4	2	6
50%	8	7	9
75%	13	10	19

Table V

Univariate analysis for factors of early death

Variable	HR	Lower limit	upper limit	P-value	N obs	N events
Discrete variables						
Syn/meta	1.143	0.670	1.951	0.6231	70	63
Total/reduced	1.171	0.455	3.013	0.7429	47	42
Continuous variables						
Bili (non-linear)				0.0190	70	63
Creat	1.098	0.348	3.466	0.8736	70	63
AST (non-linear)				0.0458	70	63
ALT	1.089	0.999	1.187	0.0524	70	63
Platelets	1.005	0.982	1.029	0.6520	70	63
CEA	1.000	1.000	1.001	0.3793	70	63
Alc phos	1.011	1.005	1.017	0.0003	70	63
Tc-scan: %shunt	1.060	0.987	1.137	0.1087	70	63
Total dose	1.000	0.999	1.001	0.5363	65	58
Tumor volume				0.0034	48	43

Multivariate analysis for factors of early death

Variable	HR	Lower limit	Upper limit	P-value	CPE
Alk phos	1.010	1.004	1.016	0.0008	0.646
Bili				0.0021	

HR: Hazard ratio
Syn/meta: synchronous / metachronous disease
Total/reduced: total/reduced dose of Y90-microspheres
Bili: bilirubin
Creat: creatinine
AST: aspartate transaminase
ALT: alanine transaminase
Platelets: platelet count
CEA: carcino-embryogen antigen
Alk phos: alkaline phosphatase
Tc-scan: Technecium scan

Lower & Upper limit: 95% confidence interval

N obs: number of observations
N events: number of events

Discrete variables: HR>1 means higher risk for the indicated category, compared to reference.
HR<1 means lower risk for the indicated category (compared to reference)

Continuous variables (linear association if not mentioned otherwise):
Units: HR is calculated for a 1-unit or 10-units increase of the level of variable
HR>1 means higher risk for higher levels; HR<1 means lower risk for higher levels
Continuous variables with non-linear effects: no HR can be estimated

FIGURE LEGENDS

Fig. 1: schematic overview of the lung shunt fraction (LSF) distribution after intrahepatic injection of ^{99m}Tc-macroaggregates (^{99m}Tc-MAA): mean of 8.3%, standard deviation of 3.5%, median of 7.8%, IQR (5.9% - 9.8%) and range (3.0% - 19.1%)

Fig. 2a-b: 61-year-old man with chemorefractory liver-only disease. a: contrast-enhanced MR imaging before ^{90}Y radioembolization shows several, small hypervascular colorectal metastases in a non-cirrhotic liver ; b: contrast-enhanced CT scan 12 months after ^{90}Y radioembolization reveals progression of disease in the left liver lobe (arrows). Note also the irregular liver contour (arrowheads) surrounded by large amount of ascites as seen in cirrhotic patients.

Fig. 3a-b: hematoxylin-eosin staining of a liver biopsy of the patient from Fig. 2: a) 25 x magnification and b) 200 x magnification demonstrates Y 90 microspheres (arrows) within portal tracts. Sinusoidal dilatation suggests severe portal hypertension.

Fig. 4: Kaplan-Meier survival curve shows an estimated survival of 65.2% (55.3% – 73.5%), 29.5% (23.6 – 35.6) and 20.2% (16.0 – 24.7) after respectively 6, 12 and 18 months. The dashed lines represent the 95% confidence interval.

Fig. 5a: preprocedural bilirubin level (X axis) related to the survival (Y axis) demonstrates a non-linear worse survival outcome in patients with low and high preprocedural bilirubin levels.

Fig. 5b: ratio of tumor volume/liver volume (X axis) related to survival (Y axis) demonstrates a non-linear better survival outcome in patients with a low and high preprocedural tumor volume/liver volume ratio.

Fig. 5c: preprocedural level of AST (X axis) related to survival (Y axis) demonstrates a non-linear worse survival outcome in patients with higher preprocedural AST levels.

Fig. 5d: preprocedural level of alkaline phosphatase (X axis) related to survival (Y axis) demonstrates a higher early mortality in patients with a higher preprocedural alkaline phosphatase level.